Complete Summary

GUIDELINE TITLE

Focal segmental glomerulosclerosis: cytotoxic therapy.

BIBLIOGRAPHIC SOURCE(S)

Thomas M. Focal segmental glomerulosclerosis: cytotoxic therapy. Nephrology 2006 Apr;11(S1):S189-93.

Thomas M. Focal segmental glomerulosclerosis: cytotoxic therapy. Westmead NSW (Australia): CARI - Caring for Australasians with Renal Impairment; 2005 Sep. 8 p. [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Focal segmental glomerulosclerosis
- End-stage kidney disease

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nephrology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the available clinical evidence pertaining to the impact of cytotoxic therapy used in combination with prednisone on renal functional decline in patients with idiopathic focal segmental glomerulosclerosis

TARGET POPULATION

Adults and children with steroid-dependent nephritic syndrome or steroid-related side effects due to idiopathic focal segmental glomerulosclerosis

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment*

1. Cyclophosphamide
2. Chlorambucil
3. Combination therapy with cytotoxics and corticosteroids

*Considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Remission of proteinuria
- Remission of focal segmental glomerulosclerosis
- Progression to end-stage kidney disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for cyclophosphamide and antineoplastic agents. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for reflux nephropathy trials not indexed in Medline.

Date of searches: 17 September 2004.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations of Others. Recommendations regarding blood pressure control targets in chronic kidney disease from the following groups were discussed: Kidney Disease Outcomes Quality Initiative, UK Renal Association, Canadian Society of Nephrology, European Best Practice Guidelines, and International Guidelines.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the levels of evidence (I–IV) can be found at the end of the "Major Recommendations" field.

Guidelines

No recommendations can be made due to conflicting Level I and Level II evidence.

Suggestions for Clinical Care

(Suggestions are based on Level III and IV sources)

Cytotoxic Therapy in Children with Focal Segmental Glomerulosclerosis (FSGS)

Cytotoxic therapy with cyclophosphamide can induce remission in children with steroid-dependent nephrotic syndrome due to FSGS, or those with FSGS with steroid-related side-effects. (Level I–II evidence, conflicting)

A number of uncontrolled studies of cytotoxic therapy in children with FSGS have reported complete remission in between 32% and 65% of cases.

- One group of authors prospectively treated 65 children with idiopathic steroid resistant nephrotic syndrome and FSGS with intravenous pulses of corticosteroids and oral cyclophosphamide. Dexamethasone (5 mg/kg) or methylprednisolone (30 mg/kg) were administered intravenously, initially as 6 pulses on alternate days, followed by 4 fortnightly and 8 monthly pulses. Oral

cyclophosphamide therapy was given for 12 weeks and tapering doses of prednisolone were administered for 52 weeks. Of 59 patients who completed the initial alternate-day therapy, 17 experienced complete remission with a further 8 having partial remission. Thirty-four (57.6%) patients did not respond to treatment. The outcome in patients receiving intravenous dexamethasone (n = 48) or methylprednisolone (n = 11) was similar.

- One group of authors described the response to cyclophosphamide in 29 steroid-resistant patients with idiopathic FSGS. Twenty of the patients were nephrotic when cyclophosphamide was started. Three of the nephrotic patients had a sustained remission of disease following treatment with cyclophosphamide. Nine nephrotic patients had partial responses. Of those responding, only one (1/9) progressed to end-stage kidney disease (ESKD). By contrast, 7 of the 8 non-responders had reached ESKD at the study completion.
- One group of authors described the response to cyclophosphamide in 26 children presenting with idiopathic focal glomerulosclerosis, 22 of whom were steroid-resistant. Ten of these patients responded to cyclophosphamide within 16 weeks of starting therapy. Seven patients relapsed after a cyclophosphamide-induced remission, however, remission could be induced with steroid therapy in five of them, despite the fact that they were previously steroid-resistant.
- One group of authors found progression to renal failure to be less frequent in children treated with cyclophosphamide.
- One group of authors reported a good response in treating steroid resistant children with chlorambucil 0.15–0.2 mg/kg/day. Of 32 children treated with chlorambucil, 66% had a complete remission of proteinuria.
- One group of authors retrospectively reviewed the management of 59 patients of FSGS with nephrotic syndrome treated with corticosteroids and/or immunosuppressive drugs as primary therapy. Twenty-seven patients were initially treated with corticosteroids alone for 9.3 months; 19 patients received corticosteroids and immunosuppressive agents associated or every other month for 5.5 months; 13 patients received either azathioprine or cyclophosphamide alone for 25 months. Remission numbers were no different from that seen in those treated with steroid alone, although fewer relapses and more sustained remissions were noted with combination therapy.

Cytotoxic Therapy in Adults with FSGS

Cytotoxic therapy with cyclophosphamide can induce remission in adults with steroid-dependent nephrotic syndrome due to FSGS, or those with steroid related side-effects. (Level III-IV evidence, conflicting)

The potential role of cytotoxic therapy in the treatment of FSGS is controversial. Overall, there have been a number of small studies that suggest the addition of cytotoxics to prednisolone results in only an extra 10% of those who do not respond to prednisolone alone. Although one study has suggested that a remission induced by prednisolone and cyclophosphamide lasts longer than one induced by prednisolone alone. (Level III-IV evidence, conflicting results)

In adults who frequently relapse after steroid therapy has been discontinued or require continuous steroid therapy to sustain the remission, cytotoxic agents can induce remission. (Level III-IV evidence, conflicting results)

- One group of authors reviewed 80 nephrotic adults with FSGS and plasma creatinine lower than 3 mg/dL. Patients were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) as primary therapy for a median of 16 and 75 weeks, respectively. Forty two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). There were no differences between steroid and cytotoxic groups.
- In a clinical series, one group of authors reported that cyclophosphamide given at a dose of 2 mg/kg/day resulted in complete or partial remission in approximately 75% of cases. However, in cases of steroid-resistance, cyclophosphamide was much less effective, with less than 25% deriving sustained benefit from an 8 to 12 week course of therapy. Similar results for treating FSGS with chlorambucil were also reported.

What Dose Should Be Used?

Where cytotoxics are to be used, therapy should be limited to a brief course only (3–4 months) because of the risk of significant toxicity, even if reduction in proteinuria is achieved. Most of the studies of cytotoxic therapy in primary FSGS have used 8 weeks of therapy. (Level IV evidence, anecdotal evidence)

Which Agent, Cyclophosphamide or Chlorambucil?

In the absence of trials comparing cyclophosphamide with chlorambucil in patients with FSGS, experience with either agent and patient characteristics should be taken into consideration when choosing which cytotoxic agent to use. (Level IV evidence, conflicting evidence)

Definitions:

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Cytotoxic therapy with cyclophosphamide can induce remission in children with steroid-dependent nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS), or those with FSGS with steroid-related side-effects.
- Cytotoxic therapy with cyclophosphamide can induce remission in adults with steroid-dependent nephrotic syndrome due to FSGS, or those with steroid related side-effects.

POTENTIAL HARMS

Where cytotoxics are to be used, therapy should be limited to a brief course only (3–4 months) because of the risk of significant toxicity, even if reduction in proteinuria is achieved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Thomas M. Focal segmental glomerulosclerosis: cytotoxic therapy. Nephrology 2006 Apr;11(S1):S189-93.

Thomas M. Focal segmental glomerulosclerosis: cytotoxic therapy. Westmead NSW (Australia): CARI - Caring for Australasians with Renal Impairment; 2005 Sep. 8 p. [15 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr

GUIDELINE DEVELOPER(S)

Caring for Australasians with Renal Impairment - Disease Specific Society

SOURCE(S) OF FUNDING

Industry-sponsored funding administered through Kidney Health Australia

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Merlin Thomas

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All guideline writers are required to fill out a declaration of conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Caring for Australasians with Renal Impairment Web site.

Print copies: Available from Caring for Australasians with Renal Impairment, Locked Bag 4001, Centre for Kidney Research, Westmead NSW, Australia 2145

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- The CARI guidelines. A guide for writers. Caring for Australasians with Renal Impairment. 2006 May. 6 p.

Electronic copies: Available from the Caring for Australasians with Renal Impairment (CARI) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on June 4, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

Copyright/Permission Requests

Date Modified: 7/27/2009